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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	PAPER NUMBER
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/804,532	CROLL-KALISH ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-16 and 18-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-16 and 18-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/19/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Examiner prosecuting this application has been changed. Any inquiries relating to the examination of the application should be directed to Examiner Singh. The telephone number is provided at the end of this office action.

Applicant's amendment filed on October 13, 2006, has been received and entered. Claims 1-13 and 17 have been canceled, while claims 14-16 have been amended. Applicants have also added claims 18-26.

Election/Restrictions

Applicants' election of claims 14-17 (Group VII) in the reply filed on October 13, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

It is noted that applicants have added new claims 18-26. Claims 18-26 that are generally directed to the elected subject matter. Therefore, these claims will be examined to the extent they encompass elected subject matter of transgenic nonhuman animal comprising an altered or deleted endogenous CIRL-3L gene.

Claims 14-16, 18-25 and 26 are under current examination.

Specification

The disclosure is objected to because of the following informalities: The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See page 21, paragraph 69. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-16, 18, 19, 21-22 and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118(a) states "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application". In the instant case, the recitation of limitation... "perseverative developmental disability (PDD) " (claims 15-16 and 21-22) is considered new matter. The specification does not provide explicit support for perseverative

developmental disability. Upon further review of the instant specification, examiner could only find support for perseverative behavior such as autism (see throughout the specification, eg. Page 5, line 1). It is emphasized that this support at best is directly to neurological disorders characterized perseverative behavior. It is also noted that instant specification provides support to pervasive developmental disorders (PDD), which may include compulsive or perseverative behavior. The specification does not provide support to perseverative developmental disability (PDD) as recited in claim 16 and 21.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph-written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981) teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time application was filed...If a claim is amended to include subject matter, limitation or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.

To the extent the claimed methods are not described in the instant disclosure, claims 15-16, 18, 19, 21-22 and 23 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since the applicants disclosure do not provide support for perseverative developmental disability (PDD) in

the specification. The specification does not provide adequate guidance on determining what is included or excluded by the claims and therefore an artisan of skill would require undue experimentation to practice or make and/or use the invention.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 14-16, 18-25 and 26 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well-established utility.

Claims 14-16, 18-25 and 26 are directed to a transgenic mouse comprising an altered or deleted endogenous Calcium Independent Receptor of Latrotoxin 3-Like (CIRL3-L) gene that is characterized by exhibiting anxiety related disorder. Subsequent claims 15-16 and 18 limit the phenotype of transgenic mouse of claim 14 to include obsessive-compulsive disorder (OCD) or preseverative developmental disability (PDD). The claims are also directed to the transgenic mouse comprising a human CIPL3-L gene. Thus, claimed embodiments are drawn to a transgenic mouse with a disruption in endogenous CIRL-3L knockout and/or additionally a human CIRL-3L knock in. Claims 21-24 limit the transgenic mouse comprising CIRL-3 to include obsessive-compulsive disorder (OCD) or perseverative developmental disability (PDD). Claims are also

directed to a method of identifying an agent capable of reducing anxiety in a mammal using the transgenic mouse of the invention. In the instant case, claimed transgenic mouse is not supported by either a specific and substantial asserted utility or a well-established utility because the specification fails to assert any utility for the claimed transgenic mouse and neither the specification nor art of record disclose any specific phenotype associated with any disease condition or model for the transgenic mouse of the invention.

The specification discloses that CIRL3-L, which is a new GPCR protein, has a role in the mediation of psychiatric disorders including anxiety disorders and schizophrenia, as well as nervous and compulsive motor activity (see paragraph 7). The disclosure states non-human transgenic animal comprising a modification of an endogenous CIRL3-L gene is generated by targeting the endogenous CIRL3-L gene with a large targeting vector. The invention embraces a knock-out wherein the CIRL3-L gene is altered or deleted such that the function of the endogenous CIRL3-L protein is reduced or ablated while it also embraces transgenic animal that is a knock-in animal modified to comprise an exogenous human CIRL3-L gene. The specification contemplate transgenic animals are useful in identifying agents that diminish anxiety or modulate other activities that are mediated by the human CIRL3-L protein (see paragraph 23). The specification teaches CIRL-3L knockout mouse were socially impaired. It is noted that specification also discloses that the severity of the impairment was dependent upon the background strain of the mice (emphasis added) (see examples and Figure 1). The knockout animal also showed gait abnormalities (example

3, figure2), impaired nociceptive responding on the hot plate test (see figure 3) and compulsive motor anxiety as evidenced by increased number of grooming bouts (see examples and figure 4). It is further noted that the instant specification contemplates transgenic animals containing a modified CIRL3-L gene are useful as animal models of anxiety-related disorders, obsessive compulsive behavior or related disorders, screening for agents capable of reducing, ameliorating and/or inhibiting psychiatric disorders, motor activity, perseverative or compulsive behaviors, and anxiety (see paragraph 63 of the specification). However, specification fails to disclose any asserted utility for the mouse as a model or for a method of identifying compound that modulated CIRL-3L in the knockout or knock in mouse model that are found to be specific and/or substantial.

At the time of filing of instant application, an artisan would have not found such utilities evident because specification does not provide a correlation between a CIRL-3 like gene and established function, phenotype or disease. The specification discloses no known function of CIRL-3L gene in the normal physiology or a known pathological state. The specification contemplates that experiments show its function in the mediation of anxiety and anxiety-related motor activity, psychiatric disorders, and the modulation of motor activity. Additionally, specification also discloses that CIRL3-L may be involved in the mediation of seizures and related disorders (see paragraph 40). The specification discloses CIRL-3L as a new GPCR homologue and it is generally known that GPCR are often the target for new therapeutics. The fact that it is new GPCR

homologue and has structural similarity does not suggest its specific function or functional importance in any disease or disease model system.

The specification of the instant application fails to provide any correlation between the disclosed phenotypes and function or role of CIRL-3L gene in any disease or any disorder. Thus, in order to determine the specific utility for the mice, the Artisan of skill would need to perform further research upon the claimed mice in order to determine the correlation between the knockouts/knock in and the observed phenotypes relating to anxiety related disorder. It is noted that specification describes CIRL3-Like is localized to many regions of the brain particularly in the thalamus and anterior cingulate cortex suggesting its role psychiatric disorders (see example 2). Ichtchenko et al (J Biol Chem. 1999 Feb 26; 274(9): 5491-8) indicated that CIRL-3 is expressed predominantly in brain similarly to CIRL-1 (see abstract). However, neither the specification nor the art disclose any known function or relationship to CIRL-3L gene to any disease. The specification also discloses a CIRL-3L knockout mouse are socially impaired suggesting CIRL-3L has a functional role in anxiety related disorder, and therefore instant knockout and knock in animal can be used as model for any anxiety related disorder more specifically PDD and OCD. It is noted that applicants conclusion that a transgenic mouse that has social impairment measured by opening field testing and CIRL3-L KO mice showing decreased sensitivity to cutaneous somatosensation suggesting a sensory gating deficits which is a common abnormalities in schizophrenia, the pervasive developmental disorders (especially autism, Asperger's syndrome, and PDD-NOS), and in attention deficit-hyperactivity disorder (ADHD) (see paragraph 73-75). It is

emphasized that open field-testing does not correlate directly to all forms of anxiety related disorder. It is noted that heterozygous mouse were never tested. It is generally known in the art that heterozygous disruption of a gene might have a wild type phenotype while mouse with homozygous disruption have an altered phenotype. In addition, any observed phenotype in homozygous disruption may be because of compensatory system that may be activated to mask the resulting phenotype. These compensatory changes may be due to differential expression of another gene, which may be regulated by the downstream product of the deleted gene (Holschneider et al. Int J Devl Neuroscience, 2000, 18: 615-618, page 615). It is emphasized that applicants do not provide any specific phenotype of expressing human CIRL-3L protein in any mouse. Thus, asserted utility of using the mice to identify drugs and using, as disease model is not substantial or creditable because specification does not identify any compound that could modulate anxiety related disorder or discloses a mouse that shows abnormalities consistent with genus of anxiety related disorders claimed in the instant application.

As set forth in the utility guideline a general statement of any specific utility, such as model for genus of anxiety related disorder or condition would ordinarily be insufficient. Similarly, a statement of utility for plurality of disease model is non-specific, renders the purported utility of the claimed CIRL-3L knockout and knock in mice to be non-specific. The usefulness of the transgenic mice, as models for disease, is not clear, absence of assessment that they reflect a particular diseases state. This leaves the Artisan of skill to speculate the uses of the mice and methods as claimed. Under the

utility guideline set forth above requirement for further research or experimentation renders the claimed invention as lacking in a specific or substantial utility. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real-world" context of use are considered substantial utilities. The evidence of record has not provided any other utility for the transgenic mice encompassed by the claims that are substantial and specific. Since the mice have no determined specific function, the relation to any disease or condition is unknown, and further, because the phenotypes in the transgenic CIRL3-L mice are not specific to any one disease or condition, the Artisan, at the time of filing, would not know how to use the mouse or any data resulting from using the mice. To make such a determination, the Artisan of skill would need to further research to mice, to determine if functions associate with CIRL3-L are present in the mice, and then identify disease or condition associated with the disclosed phenotype. The specific utilities cited in the disclosure require further research to establish whether deletion or over expression of CIRL-3L can be attributed to a particular function or utility. The invention of claims 14-16, 18-25 and 26 provide no specific and substantial utility, since no function can be attributed to the transgenic mouse of the invention.

Claims 14-16, 18-25 and 26 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14-16 and 18-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: "[W]hile the analysis and conclusion of a

lack of enablement are based on factors discussed in MPEP 2164.01(a) and the evidence as whole, it is not necessary to discuss each factor in written enablement rejection." These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Claim 14 is drawn to a transgenic mouse comprising an altered or deleted endogenous calcium independent receptor of Latrotoxin-3-like (CIRL3-L) gene characterized by exhibiting anxiety related disorders. Subsequent claims 15-16 and 18 limit the phenotype of transgenic mouse of claim 14 to include obsessive-compulsive disorder (OCD) or perseverative developmental disability (PDD). Claim 19 limits the PDD of transgenic mouse of claim 16 to include Asperger's syndrome, autism or PDD not otherwise specified or schizophrenia. The claims are also directed to the transgenic mouse comprising a human CIPL3-L gene. Claims 21-24 limit the transgenic mouse comprising CIRL-3 to include obsessive-compulsive disorder (OCD) or perseverative developmental disability (PDD). Because these claims embrace a genus of anxiety related disorder phenotype the details of the disclosure provided by the applicant, in view of the prior art, must encompass a wide knowledge so that one of skilled in the art, at the time of invention by applicant, would be able to practice the invention as claimed by the applicant without undue burden being imposed on such Artisan. This burden has not been met because it would require undue experimentation to establish to produce a transgenic mouse compromising a homozygous disruption in endogenous (CIRL3-L)

gene or a transgenic mouse comprising human (CIRL3-L) gene, wherein the transgenic mouse exhibits anxiety related disorders as claimed in the instant application.

The specification teaches that instant invention relates to a methods for identifying molecules capable of modulating CIRL3-Like (CIRL3-L) protein, therapeutic uses for such identified molecules, and animal models of human psychiatric disorders and seizure-related disorders (see para. 2 of the specification). The specification discloses that CIRL3-L, which is a new GPCR protein (see paragraph 5). The disclosure defines "CIRL3-L" protein to sequence of SEQ ID NO: 1, or a functional equivalent thereof which has at least 90%, 95%, 99% homology in the nucleotide sequence encoding the protein or the amino acid sequence. It is noted that such a functional equivalent of CIRL3-L includes substitution, addition, deletion or insertion of at least one nucleotide (see paragraph 33 of the specification). The invention embraces a knock-out wherein the CIRL3-L gene is altered or deleted such that the function of the endogenous CIRL3-L protein is reduced or ablated while it also embraces transgenic animal that is a knock-in animal modified to comprise an exogenous human CIRL3-L gene. The specification teaches CIRL-3L knockout mouse are socially impaired. It is noted that specification also discloses that the severity of the impairment depends upon the background strain of the mice (emphasis added) (see examples 3 and Figure 1). The knockout animal also showed gait abnormalities (example 3, figure2), impaired nociceptive responding on the hot plate test (see figure 3) and compulsive motor anxiety as evidenced by increased number of grooming bouts (see examples 3, and figure 4). The specification provides no evidence that a transgenic mouse carrying a homozygous

disruption of CIRL3-L gene exhibit any specific phenotype that may be described as obsessive compulsive behavior or related disorders, screening for agents capable of reducing, ameliorating and/or inhibiting psychiatric disorders, motor activity, perseverative or compulsive behaviors as compared to a wild type mouse. The specification provides working examples and guidance relating to homozygous mice whose genome comprises disruption in CIRL-3L gene. The specification teaches a number of tests that were carried out on CIRL-3L disrupted mice without providing any guidance regarding the status of functional CIRL-3L protein made in the mice. It is not apparent from the specification what is considered as wild type control. Homozygous CIRL-3L mice are compared to wild type control for multiple behavioral analysis (Example 3). The data as presented does not disclose a coherent picture of the function of CIRL-3L gene or any condition associated with CIRL-3L knockout. The specification does not provide any guidance with respect to any phenotype that is associated with transgenic mice comprising human CIRL3-L gene. The skilled artisan would have to perform undue experimentation to make and use the invention.

The art teaches the feasibility of creating a homozygous disruption of a targeted gene of interest and the creation of transgenic mouse containing the same. However, the art also teaches the resulting phenotype of a knockout mouse is exceedingly unpredictable. For example, Leonard (Immunological Reviews, 1995, 148: 98-114) discloses mice with disruption in the gc gene that was intended to be a model for X-linked severe combined immunodeficiency (XCIDS), but displays a variety of unexpected traits (Abstract). These knockout mice were expected to have thymocytes

with decreased proliferation in response to stimulation with antibodies, but the thymocytes proliferated normally (pp 105, line 7). Griffiths (Microscopy Research and Technique 1998, 41: 344-358) taught that, despite a known role for the PLP gene based on spontaneous mutations in the gene, the knockout mouse failed to display any of the expected phenotype (pp 350, last paragraph). Furthermore, the state of the art suggests such unpredictability of phenotype is correlative to the genetic background of the knockout mouse. For example, Keri et al., (Proc Natl Acad Sci U S A. 2000; 97(1): 383-7) showed elevated levels of lutenizing hormone in transgenic can result in different reproductive system abnormalities including ovarian tumors. Schoonjans et al (Stem Cells, 2003; 21:90-97), for example state that the phenotype of gene-targeted mice is not only due to genetic alteration itself but also to the genetic background in which it is generated (pp93, discussion). Similarly, Wolfer et al (Trends in Neuroscience, 2002, 25 (7): 336-340) describe the unpredictability of phenotype resulting from gene disruption can be influenced by gene flanking the disrupted coding sequence and by the general genetic background of mouse strains, wherein congenic strains carrying the same null mutation can sometime show widely divergent phenotypes (pp 336, column 1-3). In the instant case, the F2 mice homozygous for the disrupted CIRL3-L gene have genotypes from two parents, due to the recombination events during gametogensis (Gerlai, Trends Neurosci. 1996, 19(5): 177-81, pp 178, lines 1-5). These mice are genotypically different from wild type littermates, and thus wild type littermates are not good controls for the null mice (Gerali, pp 178, col. 1, lines 6-18). This effect cause "linkage disequilibrium" between the transgenic and surrounding genes, producing a 'hitchhiking donor gene

confound" (Lariviere et al J Pharmacol Exp Ther. 2001, 297(2): 467-73, pp 468, col. 1, para 3, lines 1-40) to overcome the "hitchhiking effect", two remedies are suggested: "testing a large number of mice" (Gerali pp 178, col. 2, lines 1-5) and many backcross (Lariviere, pp 468, col. 1, para. 3, lines 18-21). The specification describes data from F2 mice, except for the addition of social interaction data from the N2F2 generation, containing a higher B57B1/6 genetic background. It is noted that both generations shows social impairments, but the nature of the impairment shifted with the shift of background. Thus, in view of teaching of Gerali, it is apparent that any phenotypic alteration observed in the presently claimed CIRL3-L transgenic knockout mice could be due to genetic background (Gerali, pp 179, col. 1, lines 9-14). There is no way to tell given the tests in the disclosure thus determining whether or not the phenotype of the mice seen due to distributed gene, "hitchhiking" alleles or compensation by C57/Bl gene cannot be determined from applicants data. These observations are further supported by the studies modeling experimental seizure disorder showing the importance of genetic background of mice that may influence the transgenic or knockout phenotype as unlinked gene can have a dramatic effect on the expected phenotype (Schauwecker et al, Progress in Brain Research, 2002, 135, 139-148). Schauwecker states "modifier gene can effect the expected phenotype" (see page 142, col. 2 para. 3). Thus, at the time of filing, it is evident from the art of record that the resulting phenotype of a knockout was considered unpredictable and it is not apparent whether or not the phenotype of the mice described in the instant application is due to disrupted gene, the hitchhiking alleles or compensation by other C57B gene. The guidance provided by the

specification amounts to invitation for the skilled Artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely discloses a subset of phenotypes that fall within the broad scope of anxiety related disorder. Furthermore, mere capability to perform gene transfer in a mouse is not enabling because a desired phenotype cannot be predictably achieved by simply introducing transgene construct as recited in the claims. Holschneider et al. (Int J Devl Neuroscience, 2000, 18: 615-618) state that single genes are often essential in a number of different physiological processes. Hence, deletion of an individual gene may prove so drastic or so widespread as to create an amalgam of phenotypes whose interpretation becomes confounded by the interaction of various new physiologic changes (pp 615). Holschneider et al discuss various factors that contribute to the resulting phenotype of transgenic mice, including compensatory system that may be activated to mask the resulting phenotype; these compensatory changes may be due to differential expression of another gene, which may be regulated by the downstream product of the deleted gene. The function of CIRL3-L gene product is not completely known but has been speculated. Ichtchenko (J Biol Chem. 1999; 274(9): 5491-8) teaches that CIRL-1, CIRL-2, and CIRL-3 define a novel family of GPCRs wherein at least two of them, CIRL-1 and CIRL-2, are α-latrotoxin-binding proteins. Ichtchenko could not conclude any binding properties of CIRL-3 since he could not detect any α-latrotoxin binding of CIRL-3. However, art of record fail to establish this relationship and the specification lacks any teaching that establishes the function of CIRL3-L in the disclosed mice. In the instant case, claimed invention recite a phenotype, which may not

be related to CIRL-3L knockout given the unpredictability in the phenotype and influence of genetic background on phenotype an artisan for the specific reasons cited above it would have required undue experimentation for an artisan of skill to make and use the claimed invention.

Claims 20-24 are directed to a transgenic mouse wherein gene encoding a Human CIRL3-L is over expressed. The specification contemplates that any regulatory or other sequences useful in expression vectors can form part of the transgenic sequence. In addition specification also contemplated tissue-specific regulatory sequence(s) can be operably linked to the transgene to direct expression of the CIRL3-L protein to particular cells (see paragraph 61). The specification does not provide any guidance as to how gene-encoding CIRL3-L will be expressed in the mice. Although great advances have occurred in transgenic technology, the state of the art of generating transgenic animals is such that the resulting phenotype would not be predictable. This is because the art of transgenic animals has for many years stated that the unpredictability lies with the site or sites of integration of the transgene into the target genome. Transgenic animals are regarded to have within their cells cellular mechanisms which prevent expression of the transgene, such that DNA methylation or deletion from the genome (Kappell et al Current Opinions in Biotechnology 3, p. 549, col 2, par 2, 1992). The elements of the particular construct used to make transgenic animals are held to be critical, and that they must be designed case by case without general rules to obtain good expression (e.g. specific promoters, presence or absence of introns, etc. (Houdebine J. Biotech 34:281, 1994). Furthermore, Cameron et al

(Molecular Biotechnology 7: 253-265, 1997) noted, " Well regulated transgene expression is the key to successful transgenic work, but all too often experiments are blighted by poor levels or complete absence of expression, as well as less common problems, such as leaky expression in non targeted tissues. A feature common to any transgenic experiments is unpredictable transgenic lines produced with same construct frequently displaying different levels of expression. Further, expression levels do not correlate with number of transgene copies integrated. Such copy number independent expression pattern emphasizes the influence of surrounding chromatin on the transgene" (pp 256; section 4 on transgene regulation and expression). Sigmund states that the random nature of transgene insertion, resulting founder mice can contain the transgene at a different chromosomal site, and that the position of the transgene effects expression, and thus the observed phenotype (Sigmund et al Arteroscler Throm Vasc Biol 20:1426, col 1, par 1, lines 1-7, 2000). With regard to the importance of promoter selection, Niemann states that transgenic pigs made with different promoters regulating expression of growth hormone gene give disparate phenotypes, one deleterious to the pig, the compatible with pig health (Neimann Trans Res 7:73, col 2, par 2, line 12 to p. 73, col 1, line 4, 1998). While the intent is not to say transgenic animals of a particular phenotype can never be made, the intent is to provide art taught reasoning as to why the instant claims are not enabled. Given such differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for any transgenic mice, it would have required undue experimentation to establish the levels of the transgene product, the consequences of that product, and therefore, the resulting

phenotype. The specification fails to provide teachings or specific guidance to overcome the above-described unpredictabilities, in order to successfully produce transgenic mice with a specific anxiety related disorder phenotype and as such, the claims are not enabled.

Claims 25-26 are directed to a method of identifying an agent capable of reducing anxiety in a mammal by administering a test agent to the transgenic animal of the instant invention. The disclosure provided guidance in terms of expression level of CIRL-3L in brain but it does not detail provide any guidance in terms of its functional involvement in anxiety related disorder nor does it disclose a relationship to a condition associated with anxiety that could be treated by any agent identified by the instant methods. Therefore, because an artisan does not know the function of CIRL-3L and does not know of any known relationship to a disease or condition, and artisan would not know how to use any identified compounds. Furthermore, for an artisan to use or make the instant method for its intended use, an artisan would have to determine the function of CIRL3-L and if there are any disease or specific conditions associated with CIRL-3L. Therefore, given the act that an artisan would not know how to make or use the instant method for identifying an agent that reduces anxiety. It is emphasized that the specification does not provide any specific guidance for the use of a method for identifying agents that treat any particular disease. The specification teaches that agents identified through the screening method of the invention are potential therapeutics for use in a number of conditions including decreasing anxiety, nervous or compulsive motor activity, perseverative behaviors, and/or regulating psychiatric

abnormalities such as anxiety disorders and schizophrenia, or neurological disorders such as autism or Tourette's syndrome, as well as in the treatment of seizures and related disorders (see specification paragraph 45). Tecott et al (Am J Psychiatry 160:646-656, 2003) while reviewing the mouse behavioral models of psychiatric illnesses state "it is noteworthy that the assays of rodent depression- and anxiety-related behavior just discussed may be considered to model particular behavioral states rather than the full range of affective, cognitive, and neurovegetative symptoms characteristic of common psychiatric disorders. As discussed in other contributions to this issue, susceptibilities to these illnesses are polygenically determined, and the environmental contributions to their pathophysiology are incompletely understood. Therefore, current mouse models may be most productively used to examine the biological bases of individual features of psychiatric disorders rather than as comprehensive models of complex psychiatric syndromes (see page 653, col. 1, para. 2). It is noted that specification does not provide any specific teaching regarding how individual symptoms are related specifically to any condition or type of agents, amount needed, dosage schedule and delivery route that would be used to identify the agent. An artisan would have to perform undue experimentation to first establish a link between the transgenic animal with a specific condition and then test various parameters using different type of agents, dosage and delivery route in order to reduce symptoms seen the transgenic animal of the invention. It is emphasized that behavioral symptoms in disease or condition can be cause by a variety of mechanism that may or may not have any involvement of CIRL-3L gene. Given that the specification and art do

not disclose an known disease causes by impaired or over expression of CIRL-3L, an artisan would not know if the instant mice represent a model for anxiety related disorder that would be applicable to a disease or condition associated with anxiety. Furthermore, an artisan would not know if the any particular agent identified using the knock in mouse would be able to treat a disease symptom similar to those observed in the knockout mouse. An artisan would have to do further experimentation to determine if the symptoms associated with the knockout as associated and therefore representative a disease. In view of foregoing discussion, it is apparent that any difference of symptom seen in the instant transgenic mouse cannot be generally associated with any complex psychiatric disorder. Therefore, an artisan would not know if the compounds identified by measuring behavioral testing in the transgenic mouse of the invention would be effective for its intended use in the treatment of genus of psychiatric disorder as contemplated in the instant application.

In view of the lack of teachings or guidance provided by the specification with regard to an enabled transgenic mouse comprising an altered or deleted endogenous CIRL3-L gene, the lack of teaching or guidance provided by the specifications to overcome the art recognized unpredictability of expression pattern, resulting phenotype and for the specific reasons cited above it would have required undue experimentation for an artisan of skill to make and use the claimed invention. It would require undue experimentation for an Artisan to make and use the claimed invention and/or working examples demonstrating the same, such invention as claimed by the applicant is not enabled for the claimed inventions.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14-16 and 18-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 14 is indefinite to the extent it recites a limitation comprising an altered or deleted endogenous CIRL3-L. In the instant case, it is unclear gene encoding protein of the invention is altered to what extent. In addition, whether instant phrase is limited to a mouse without any of CIRL-3L gene or if the phrase embraces a mouse without any of the coding sequence of the CIRL3-L gene, a mouse with a disruption in the CIRL-3L gene resulting in no functional CIR3-L protein, or a mouse with a disruption in CIRL-3 leading to less than normal amount of functional CIRL3-L. The meets and bounds of claimed invention cannot be determined. Claims 15-16 and 18-26 are directly or indirectly dependent on claim 14. Appropriate correction is required.

The meets and bounds of the phrase "characterized by" in claim 14 is indefinite to the extent it is unclear if the claim is limiting to the phenotype of anxiety related disorder or limiting how the mouse is tested for anxiety related disorder. It is unclear if the mouse has anxiety related disorder or it means mouse shows sign relating to an

anxiety related disorder to different behavioral testing. Claims 15-16 and 18-26 are directly or indirectly dependent on claim 14. Appropriate correction is required.

Conclusion

No Claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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